

REMARKS

The Claims in the case are Claims 26-32. The claim language both concisely claims Applicant's invention for which patent protection is sought, and it avoid the indefiniteness, obviousness and novelty issues against the claims in the rejection. The Examiner is respectfully requested to reconsider and withdraw the rejections for the following reasons.

Support for the claims 26-32 is found in the specification, at p. 9, which describes the folding conditions. Applicant teaches the presence of two components in the folding buffer, the DMSO and/or DMSO/DMF component, and the reduced glutathione. Applicant teaches these components also in Examples 4 and 5. Nowhere in the specification are any other components described or taught. The specification and support for these claims dates from the earliest filing date.

Applicants are entitled to the same effective filing date of the parent application and SECTION 102 and SECTION 103 rejections should be reconsidered and withdrawn

This case claims a method of folding TGF- β 's using a folding buffer consisting essentially of glutathione in its reduced form and an organic solvent which is DMSO (Dimethylsulfoxide) or DMF (Dimethylformamide) or a mixture of DMSO and DMF. There is no presence of other components: mild detergents such as CHAPS or CHAPSO, or any chaotropic agents or any copper or manganese salts. The absence of any additional materials in the folding buffer is constrained by the language "consisting essentially of".

The Examiner is correct that Applicants, to be entitled to the earlier filing dates, must have the claimed invention disclosed in the parent applications. There should be no subject matter added or additional disclosure claimed not presented in the prior applications. All these conditions are met. In addition, the invention is found in the earlier applications. The inventorship remains as originally filed and is correct.

All the claims in the case are entitled to all dates in the chain of pendency claimed under 35 USC 120 and 119. The earliest filing date in the chain of pendency, is the EPO filing date of 25 July 1994; the continuity flows through all the intervening co-pending applications. This issue had been raised by the Examiner, regarding the phrase "the substantial absence of either a chaotropic agent or a copper or manganese salt". This phrase is not now in the claims in the instant application. The claim language in the newly added claims is drawn around the express teaching found in the instant application, that the process conditions do not contemplate the presence of extraneous reagents than those disclosed and claimed. The issue arises out of the rejection of the claims over the Builder reference.

The Examiner had rejected the Claims 37-45, and 47-53 under 35 USC § 102 (e), as anticipated by Builder, US 5 407 810. The Examiner had also rejected Claims 37 and 46, 35 USC § 103 (a), as being unpatentable over Builder, US 5 407 810. Reconsideration of the rejection of the claims in the application in view of the amendments made to the claims and the following arguments is respectfully requested.

Applicant's invention does not use either of these two latter components in the folding buffer, at least for TGF-beta 3. There is acetic acid in the TGF-beta solution which is then mixed with the folding buffer. However, the acetic acid solution which is used by Applicant, (see Example 3-5 of the application) does not amount to presence of a chaotropic agent in the buffer. It provides acidic conditions for solubilization. Solution fractions containing the solubilized acidified monomeric TGF- β are then directly subjected to in vitro folding, but the folding solution does not contain a chaotropic agent.

Applicant also does not add Cu or Mn salt, which have as their general purpose, the facilitation of the generation of disulfides, e.g., cystines from the reduced cysteine sulfhydryl groups. Instead, Applicant employs a 5 mM reduced glutathione. Because of its chemical nature (free sulfhydryl group), this agent facilitates disulfide formation by a different chemical mechanism, catalysis of sulfhydryl/disulfide interchange, quite unobvious from the method used in Builder.

SECTION 102 and SECTION 103 rejection: Builder US 5,407,810, in view of Rudolph

The Examiner had rejected the Claims 37-45, and 47-53 under 35 USC § 102 (e), as anticipated by Builder, US 5 407 810. The Examiner had also rejected Claims 37 and 46, 35 USC § 103 (a), as being unpatentable over Builder, US 5 407 810. Reconsideration of the rejection of the claims in the application in view of the amendments made to the claims and the following arguments is respectfully requested.

The Builder patent, US 5 407 810 has its main emphasis on a multi-phase extraction procedure. It also covers a folding process in which a solubilized protein, such as TGF-beta, is treated with a folding buffer which comprises a polar aprotic buffer, including DMSO or DMF. In addition, however, the Builder folding buffer comprises a number of additional essential components, including about 0.1 to 9M of a chaotropic agent and about 0.01 to 17 microM of a copper or manganese salt.

As noted above, Applicant's invention does not use either of these components taught as necessary in Builder in the claimed folding buffer, at least for TGF-beta 3. There is acetic acid in the TGF-beta solution which is then mixed with the folding buffer. However, the acetic acid solution which is used by Applicant, (see Example 3-5 of the application) does not amount to USSN 09/813,271, filed 03/20/2001 - 4 -

presence of a chaotropic agent in the buffer. It provides acidic conditions for solubilization. Solution fractions containing the solubilized acidified monomeric TGF- β are then directly subjected to in vitro folding, but the folding solution does not contain a chaotropic agent.

The Rudolph reference relates to protein folding in general. Although Rudolf does not specifically relate to TGF- β s, he does teach the value of e.g., many thiols, including both reduced and oxidized glutathione as "oxido-shuffling" reagents. The clear implication of Rudolph is that the thiol class of chemicals could serve some useful purpose in attempts to form "correct" disulfide bonds. It is a big leap forward, however, to do as the Examiner has done in the rejection, to say that the combination of Builder with Rudolph makes Applicant's invention "obvious". The combination of the references does not make Applicant's invention obvious, and should be reconsidered and withdrawn.

Applicant also does not add Cu or Mn salt, which have as their general purpose, the facilitation of the generation of disulfides, e.g., cystines from the reduced cysteine sulfhydryl groups. Instead, Applicant employs a 5 mM reduced glutathione. Because of its chemical nature (free sulfhydryl group), this agent facilitates disulfide formation by a different chemical mechanism, catalysis of sulfhydryl/disulfide interchange, quite unobvious from the method used in Builder. Nothing in the Rudolph reference, in combination with Builder, makes the very particular combination of reagents claimed in the instant application

The conditions described are present in the new Claims in the instant application, which, it is urged, are patentable over the cited art. Reconsideration and withdrawal of the rejection is respectfully requested.

SECTION 102 rejection over Cerletti WO 96-03432

This rejection is incorrect and should be withdrawn, in view of the fact that Applicant is entitled to the 25 July 1994 filing date in the chain of co-pendency.

OBVIOUSNESS-TYPE DOUBLE PATENTING rejection over Cerletti US 6,057,430

The Claims have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending application USSN 09/123 233, which is issued as US Patent 6 057 430. Applicant had filed a terminal disclaimer of any portion of the term of a patent issuing out of the instant application over the term of the US Patent 6 057 430, and a copy of those papers, which were separately filed on January 17, 2001 in parent application USSN 09/316,724, are enclosed herein. The Examiner is respectfully requested to reconsider and withdraw this ground of rejection.

Section 112 issue

The issue regarding the improper dependency of the claims is mooted in the newly added claims, and should be withdrawn.

Conclusion

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Should the Examiner feel that telephonic communication with Applicants' representative would further the prosecution of the instant application, he is invited to telephone the undersigned.

No fees are believed due with this amendment; if however, any fees are due, please charge such fees to Deposit Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,



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Enclosure: copy of terminal disclaimer, separately filed on 1/17/01